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REVIEW ARTICLE

The management of leprosy reversal reactions

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Introduction

Although *Mycobacterium leprae* infects both skin and peripheral nerves, it is the propensity to nerve damage with resulting disability which marks leprosy as a significant health problem. There have been recent dramatic falls in the prevalence of leprosy following the implementation of multi-drug therapy (MDT) of short fixed duration;[1,2] however, the incidence of new cases has yet to fall significantly in the major endemic countries and the pool of patients with potential nerve damage remains large.[3] Leprosy reactions impact significantly on the management of the disease in two ways. First, the major determinant of nerve damage is inflammation occurring within the perineurium, and this is exacerbated during reactional episodes. Second, the spontaneous and fluctuating course of reactions, often with deterioration occurring after the commencement of MDT, is baffling to the patient and medical worker alike and a significant barrier to compliance. Understanding the mechanisms and natural history of reactions is critical for the early treatment and prevention of nerve damage.

In leprosy, host immunity to the bacillus determines the pattern of the disease,[4] with a spectrum of response. In tuberculoid leprosy (TT), a strong cellular immune response to *M. leprae* limits replication of the organisms, but causes tissue damage to a small number of nerve trunks and skin lesions. The hallmark of lepromatous leprosy (LL) is the absence of T cell recognition of the organism, resulting in uncontrolled proliferation of bacilli, numerous skin lesions and infiltration of dermal nerves and nerve trunks. The bulk of patients have borderline leprosy with retention of some T cell responses and moderate numbers of bacilli and lesions. Although patients with the polar TT and LL forms of the disease are generally stable, in the absence of therapy there is a gradual decline in the cellular immune response in the majority of patients, so that they downgrade to a more lepromatous form of disease. Against this background, spontaneous fluctuations in the immune response are responsible for leprosy reactions. Type 1 reactions are usually 'upgrading' or reversal reactions (RR) and caused by an increase in cell-mediated immunity to the bacilli in dermal macrophages and Schwann cells, leading to inflammation of skin and nerve trunks. They may occur throughout the whole leprosy spectrum, but are most common in borderline patients. Previously, a

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downgrading form of type 1 reactions was described in untreated patients, but these are rarely if ever encountered now and will not be discussed further. Type 2 reaction or erythema nodosum leprosum (ENL) is a systematic inflammatory response to the deposition of extravascular immune complexes and occurs in LL and borderline lepromatous (BL) patients. The management of ENL has recently been discussed,[5] and in this review, the management strategies for RRs in the light of the underlying immunopathology will be discussed.

Prevalence of reversal reactions

Despite the importance of RRs in inducing nerve damage, estimates of their prevalence and incidence are difficult to obtain because of differences in the case definitions used and the patient population surveyed and the retrospective nature of most studies. The epidemiology of RR has been reviewed[6] and, overall, the cumulative prevalence of RR varies from 8 to 33% for all leprosy patients. Common patterns have emerged which are relevant to interpreting the results of RR treatment in different settings.

1. RRs are more frequent in studies conducted in referral centres compared to field trials, reflecting the more advanced disease in referred or self-reporting patients. For example, in centres in Thailand and Nepal 32 and 26·9% of patients developed RR,[7,8] while in a recent field study in Bangladesh, only 8·8% of patients experienced RR.[9]
2. The type of leprosy affects the risk of RR, so that patients with borderline (BB) and BL leprosy have a higher prevalence than borderline tuberculoid (BT) patients. For example, in a field study in Ethiopia, the incidence rate for RR in paucibacillary (PB) leprosy was 13·1/100 patient years at risk (PYAR) compared to 28·4/100 PYAR in multibacillary (MB) patients.[10]
3. Patients with more extensive diseases, as assessed by the number of body areas[7] or pre-existing nerve function impairment (NFI),[10] are more likely to develop RRs leading to further tissue damage, and these patients have a less satisfactory response to therapy.
4. RR can occur at any time during treatment, being present at diagnosis in 2–5% of patients in Africa[6] and 30–47% in Nepal and India.[7,11] The highest risk is during the first year of treatment, with up to 80% occurring in the first 6 months of MDT,[12] but RR can occur later, particularly in BL patients.[13] Importantly, RR may emerge after the completion of MDT. In Ethiopia,[14] 10·2 and 7·8% of BT patients experienced RR before and after 6 months of MDT, respectively, compared to 22·8 and 10·7% of multibacillary (MB) patients before and after 2 years of MDT in India.[15] Both these studies have confirmed the clinical impression that relapses of RR is common, with up to a third of RR patients having recurrences.

Immunopathology of reversal reactions

Understanding the immunopathology of RR allows the rational use of appropriate therapy. Analysis of the skin lesions from patients in reaction have defined the cellular inflammatory processes,[16] although the factors triggering the characteristic increase in cellular reactivity to *M. leprae*[17] are still poorly understood. The tissues are infiltrated predominantly with $CD4^{+}\alpha\beta$ T cells, although $\gamma\delta$ T cells are also present,[18] with accompanying oedema and

increased expression of adhesion molecules on endotheliam and overlying keratinocytes.[19] This influx of lymphocytes and monocytes produces localized delayed type hypersensitivity (DTH) reactions in the skin and nerves. The presence of activated T cells in reactional lesions results in elevated IL-2 receptor levels in blister fluid from lesions.[20] There is a dramatic increase in the number of interferon-γ (IFN-γ) expressing cells and levels of IFN-γ mRNA in reactional lesions.[21] Analysis of T cell clones derived from skin biopsies before and after the development of RR confirmed the shift to a polarized pattern of cytokine release dominated by IFN-γ during RR.[22] Intriguingly, higher levels of mRNA and protein for tumour necrosis factor (TNF) are present in reactional nerves than skin lesions.[23] Nerve function is impaired by the local ischaemia secondary to the compression of perineural blood vessels by the inflammatory oedema and by direct destruction of Schwann cells and axons by the $CD4^+$ T cell-mediated granulomatous process (Figure 1).[24] With time, post-inflammatory fibrosis leads to irreversible nerve damage. The intensity of the localized inflammation is reflected by raised serum levels for TNF,[25] soluble IL-2 receptors[26] and adhesion molecules.[27] The institution of effective anti-inflammatory therapy rapidly reverses these abnormalities.

Clinical issues in management

RR may take the form of one or more of the following:

1. Increased inflammation with swelling and erythema in established skin lesions, or in BL and subpolar LL patients, in newly appearing lesions.
2. Acute inflammation in affected nerve trunks with tenderness and pain over the nerve and loss of motor and/or sensory function in its distribution.
3. Recent (<6 months) and/or progressive loss of motor or sensory function in the absence of painful neuritis.

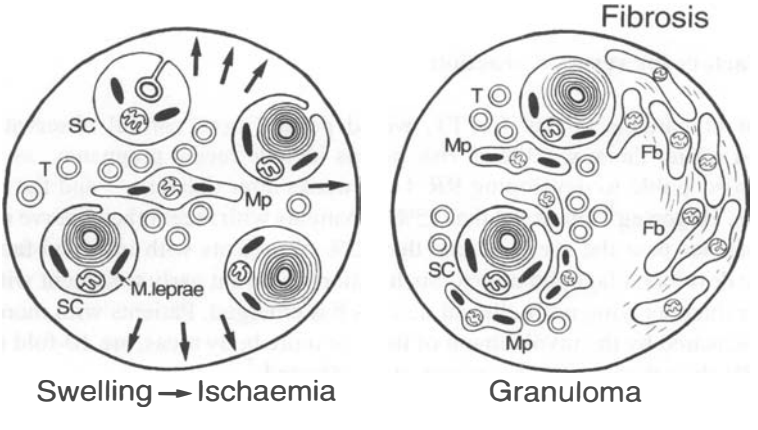

Figure 1. Mechanisms of nerve damage in reversal reactions. The influx of T lymphocytes (T) and macrophages (Mp) with resultant oedema causes swelling and secondary ischaemia to the nerve. *M. leprae*-infected Schwann cells (SC) and axons were also destroyed directly by the T lymphocyte-driven granulomatous response to chronic antigenic stimulation. Fibroblasts (Fb) are responsible for post-inflammatory fibrosis which can cause continuing nerve damage after the features of inflammation have subsided.

Education of patients and staff is vital for the early recognition of RR. All newly diagnosed BT, BB and BL patients should warned of the possibility of RR during treatment and the importance of immediate presentation to enable prompt therapy. Staff should be trained to examine for the features of NFI at each visit, using simple screening procedures for voluntary motor testing (VMT) and sensation. There is considerable variation in the methods used for detecting NFI, and the frequency and care in testing will influence the number of patients detected with NFL. Recent comparisons of different methods for detecting sensory impairment demonstrated that testing with multiple nylon monofilaments or for two-point discrimination were more sensitive than simple pin-prick sensation.[28] The major source of variability between testers was testing skill and experience, emphasizing the importance of staff training. The challenge is to standardize simple and reproducible tests for implementation in field programs so that the majority of leprosy patients will benefit. This is particularly relevant to the management of leprosy patients in general health services where medical staff are less familiar with leprosy complications.

At initial assessment or on serial testing, some leprosy patients will be detected with NFI and no other features of typical RR. There has been confusion as to whether these patients have RR and warrant treatment and the phenomenon has been referred to as 'quiet nerve paralysis' or 'silent neuritis'. In a retrospective analysis of 536 patients in a referral centre, 7% of new patients had silent neuropathy and its incidence rate was 4·1 per 100 PYAR with 75% of episodes occurring in the first year.[29] Although cell-mediated inflammation is probably the major aetiological factor, Schwann cell dysfunction and post-inflammatory fibrosis may also contribute to this silent neuropathy and some studies now identify patients with NFI and RR separately. In a field study in Bangladesh,[9] the incidence rate of NFI was 3·5/100 and 7·5/100 PYAR in PB and MB patients, respectively, compared to rates for 'clinical' RR of 1/100 and 6/100 PYAR, respectively. Further studies are required to define the epidemiological significance and natural history of this group. However, as the motor and sensory function in the affected nerves improves significantly with corticosteroid therapy, inflammatory damage must be a significant factor and these patients can be operationally considered with RR patients for diagnosis and therapy.

Predictive factors for reversal reaction

Identification of patients at risk for TT, would permit more careful observation of this subgroup and earlier therapy. Clinical risk factors include recent pregnancy, as women are particularly susceptible to developing RR 4–12 weeks after delivery,[13] and the presence of facial plaques. Hogeweg[30] observed that 85% of patients with recent facial nerve damage had significant patches near the eye, and also that 45% of patients with inflamed facial patches subsequently developed lagophthalmos. Such patients warrant early treatment with corticosteroids rather than delaying until clinical neuritis has emerged. Patients with more extensive disease, as measured by the involvement of three or more body areas, are 10-fold more likely to develop RR than those with one or two areas affected.[7]

RRs are a manifestation of increased cell-mediated immunity to *M. leprae*, and although increased serum levels of some cytokines and soluble receptors occur during RR, these cannot be used to predict the onset of RR. The levels of *M. leprae*-specific antibodies correlate with the bacillary load and clinical extent of disease.[31] When borderline leprosy patients had both anti-*M. leprae* phenolic glycolipid IgM antibodies and a positive lepromin

test, as evidence of T cell responsiveness to *M. leprae*, there was a significant increase in the cumulative prevalence of RR to 78% compared to 31% in all borderline patients.[12]

Roche[32] has analysed a cohort of 534 Nepali borderline leprosy patients for risk factors, present at the start of treatment, which predict the development of RR at any stage during therapy. Of the 12 parameters analysed by logistic regression, three were independently associated with a significant risk of subsequent RR. These were the presence of facial lesions [adjusted odds ratio for RR (AOR) = 4·6], involvement of three or more body areas (AOR = 2·2) and positive IgM anti-PGL antibodies (AOR = 1·72).[32]

A final clinical issue is distinguishing between late RR and relapse in patients who have completed MDT, particularly in skin smear negative PB patients. Clinical criteria for differentiating the two have been proposed[33] and skin biopsy where available may assist. However, it may not be possible to differentiate between the two conditions in all patients. Operationally, patients with increased NFI should be treated with a full course of corticosteroids and either MDT, if there is any possibility of relapse in smear positive patients, or a single drug, preferably clofazimine 50 mg daily, in smear negative patients.

Current management of reversal reaction

The principles of management for RR are maintenance of anti-mycobacterial drugs, effective and prolonged anti-inflammatory therapy, and adequate analgesia and physical support during the phase of active neuritis. It is imperative that MDT is maintained after the onset of RR, as reduction in the antigenic load in skin and nerves removes the target for the T cell-driven inflammation and lessens the propensity to recurrence.

Corticosteroids

Although there is a paucity of controlled trials assessing therapy for RR, there is a consensus that corticosteroids form the cornerstone of drug therapy. Some authors recommend a staged approach to therapy with a trial of aspirin and/or hydroxychloroquine for 'mild reactions' involving the skin alone without nerve impairment.[13,34] This approach may be counter-productive, as the definition of this subgroup is arbitrary and there are no studies in RR showing that this conservative therapy is effective or prevents progression to nerve damage. It may have arisen from a reluctance to use corticosteroids when this required hospital admission and from an under-estimation of accompanying nerve damage detected by routine clinical examination. For example, 19% of patients with neuritis in one nerve have significant slowing of motor conduction in other clinically unaffected nerves.[35] Moreover, full recovery of nerve function does not occur in a significant proportion of RR patients despite corticosteroid therapy. Therefore the early use of corticosteroids is recommended once there is unequivocal evidence of increased inflammation in established or new skin lesions, NFI of <6 months duration or tender nerves. The earlier effective therapy is instigated, the more likely permanent nerve damage will be prevented.

Corticosteroids modify the course of RRs in a number of ways. They reduce cutaneous and intraneural oedema, leading to a rapid improvement within days in some patients and also reduce post-inflammatory scar formation during the prolonged healing phase.[36] Their chief effect, however, is to suppress the T cell-driven inflammatory response to *M. leprae* antigens

within the skin and nerves. Therefore, immunosuppressive doses of corticosteroids are required for prolonged periods as the reaction will persist whilst the bacillary load gradually falls. Although the optimal doses and duration of therapy have not been established by clinical trials, the recommended regimens reflect these principles. Rose and Waters[13] and Naafs[36] recommend an initial dose of 40 mg of prednisolone (or prednisone). This is sufficient to control most RRs; however, patients with severe NFI and no response after a week may require a higher dose of 60 mg (or 1 mg/kg) and occasionally further increases up to 120 mg to control nerve symptoms. Although some authorities recommend a starting dose of 60 mg prednisolone,[37] field studies with fixed regimens indicate that a dose of 40 mg prednisolone is sufficient to control 85% of RRs.[14] A retrospective comparison of four corticosteroid regimens used in Nepal demonstrated that there were no differences in outcome for regimens starting with dexamethasone 6 mg, prednisolone 30 mg twice daily or prednisolone 60 mg once daily, both reducing over 6 months, or prednisolone 40 mg daily reducing over 4 months.[38] Once there is evidence of improvement, the dose of prednisolone can be reduced at about 5 mg every 1–2 weeks until 20 mg is reached. This is usually continued for some months while more gradual improvement occurs[39] until optimal nerve function has been obtained, and then the drug withdrawn at 5 mg per fortnight. The maximum improvement occurs in the first 3 months, but may continue for up to 6 months.

In ideal circumstances, the length and dose of therapy is individualized based on careful assessment of motor function by VMT and sensitive tests of sensory function, such as the nylon monofilament test.[28] Generally, most BT patients require prednisolone for 4–9 months, BB patients for 6–9 months and BL patients for 6–18 months and even 24 months.[13] One comparative trial demonstrated that prednisolone therapy of longer duration (3–18 months) was superior to short courses of therapy (2 months) for recovery from motor impairment.[40] More recently, 12 weeks of prednisolone therapy for RRs in BB/BL patients was found to be inadequate, with one-third of patients relapsing; however, extension of therapy to 20 weeks resulted in a low recurrence rate.[14]

The recognition that ambulatory therapy with corticosteroids is both effective and safe has been a major advance in the management of RR. Ideally, RR patients should be admitted to hospital, but adherence to such a policy may limit the use of corticosteroids to only a minority of those who require RR treatment. This approach was first demonstrated by Kiran,[41] who observed improvement of 66% of affected nerves in 33 patients treated with prednisolone 25 mg as the initial dose for an average of 5 months. Subsequently, in a larger field study in Ethiopia, standardized courses of 12 weeks and 20 weeks (both starting at 40 mg prednisolone) were used for both RR and ENL reactions in BT and BB/BL patients.[4] Patients with severe ENL, recurrent reactions, deteriorating nerve function despite corticosteroids or associated medical problems were referred for hospital therapy, along with patients in whom late RR could not be distinguished from relapse after completing MDT. Nevertheless, 85% of all RR patients selected by these criteria could be treated at home. Of these 161 patients, 88% showed improvement in nerve function. Even allowing for the exclusion of patients with severe or recurrent reactions, this compares favourably with recovery rates for RR following hospital treatment. These range from 63% for improvement in affected nerves in BT and BL patients receiving a fixed regimen of 6 months prednisolone starting at 40 mg daily[42] to 50% for improvement in neuritic episodes when lower doses of prednisolone were used for shorter periods.[11] Following four regimens of high dose corticosteroids for 4–6 months, the recovery rates varied from 30 to 84%, depending on the nerve involved.[38]

A variety of factors influence the response to corticosteroids. The level of nerve

impairment at the initiation of therapy has a major bearing on outcome. Only 35% of patients with complete anaesthesia and 11% with motor paralysis improved to good function at 3 months, compared to 67% and 55% for patients with moderate impairment.[38] Remarkably similar outcomes were obtained in severe or moderately affected patients after corticosteroids alone or combined medical and surgical treatment.[43] Patients with recent NFI, of less than 6 months duration, demonstrate greater improvement in nerve function than those with old impairment, and this is the usual time limit set for the instigation of reaction therapy in patients with NFI alone.[14] Whilst also observing maximum recovery in those with recent NFI, van Brakel and Khawas[38] did note significant improvement in sensory function after 3 months prednisolone therapy in some patients with NFI of over 6 months duration. Studies are required to determine if this group of responsive patients can be defined more accurately. The leprosy type also affects response and two studies have reported significantly better recovery in BL than in BT patients.[38,42]

There are also differences in the rate of recovery for different nerves. In five separate studies a higher proportion of patients with median nerve damage recovered motor and sensory function than those with ulnar nerve damage.[14,38,41,42,44] Improvement in recent facial nerve paralysis was observed in 70–75% of patients in two studies using standardized corticosteroid regimens;[14,15] however, in another study therapy, this resulted in recovery in only 30% of these,[38] emphasizing the importance of early treatment.

Patients with 'silent neuritis' also respond to corticosteroids. Srinivasan[44] initially observed that in a small group of 25 patients with 'silent neuritis' 75% recovered motor function, 83% in those with paralysis of <13 weeks and 53% when the paralysis was of longer duration. In Nepal, motor and sensory function in nerves affected by silent neuropathy also improved significantly after 3 months of prednisolone therapy.[29] In a recent field study in Bangladesh, 100 patients with recent NFI (<6 months duration) were treated with fixed duration prednisolone (starting dose 40 mg, for 16 weeks) regardless of whether other features of RR were present. Using conservative measures of change (at least 2 points in motor/sensory scores) 65 and 48% of patients showed improvement in sensory or motor function, respectively, and this improvement persisted for >6–8 months after therapy.[46] Therefore patients with NFI alone can be successfully and safely treated with fixed duration therapy in the community, but a significant proportion of patients still fail to respond. The broader application of corticosteroids in ambulatory settings has not been associated with an increase in complications of treatment, but careful pre-assessment for other diseases is important.[47] In particular, infections such as tuberculosis, amoebiasis and strongyloides may be exacerbated by corticosteroid therapy and these should be excluded or treated as necessary.

Other therapies for reversal reaction

What other therapeutic options are available for RR? Patients with severe neuritis and pain may require hospitalization for parenteral narcotics and splinting of the affected limbs.[34] Clofazimine is an important component of MDT for MB leprosy and may contribute some anti-inflammatory effect.[37] This value is less marked in RR than ENL, and in particular, clofazimine is not effective in the acute phase of RR. Therefore, the dose of clofazimine is usually unchanged during therapy for RR. Clofazimine may have a prophylactic role against RR. In a recent study, borderline leprosy patients considered to be at a high risk for RR, who

received a modified MDT regimen with initial higher doses of clofazimine (300 mg/day compared to 50 mg for the first 12 weeks), experienced a significant reduction in RRs over 2 years (5·7%) compared to that observed in a retrospectively chosen control group (26·1%).[48] This finding warrants a properly controlled prospective trial to determine if this regimen should be more widely implemented.

Azathioprine has been employed both as an immunosuppressant and for its steroid-sparing effect. In a small study, a slightly higher proportion (90%) of patients receiving azathioprine (1 mg/kg) and prednisone for 6 months demonstrated greater motor improvement than those receiving prednisone (77%) or azathioprine (79%) alone.[49] As azathioprine acts slowly and has no effect on intraneural oedema, it should only be used as an adjunct after initial treatment with corticosteroids.

Cyclosporin A is a potent immunosuppressant which acts directly on $CD4^+$ T cells and has proven benefit in controlling transplant rejection and graft versus host disease. There are case reports of its value in controlling severe steroid-unresponsive RR with the response to cyclosporin (7 mg/kg) being evident at 10 days[50,51] and it may be as effective as corticosteroids in patients with untreated RR. However, its expense limits its availability and use in leprosy endemic countries.

Surgery with decompression of the epineurium of swollen nerves has been previously advocated for patients with persistent nerve pain despite corticosteroid therapy. Although this may improve nerve conduction and function in individual cases, enhanced benefit has not been confirmed in clinical trials. Recent analysis of a randomized comparative trial of corticosteroids and surgical intervention in 39 patients with early neuritis showed that decompression of the ulnar nerve and medial epicondylectomy with medical therapy had no additional benefit over corticosteroids alone at follow-up after 1 or 2 years.[43] Therefore surgery should be reserved for the rare situations of nerve abscess in BT and TT patients or intractable pain despite vigorous immunosuppressive therapy.

Future approaches to management

Improvement in outcome for nerve function in RR in the immediate future will probably derive from the optimal use of current drugs, particularly corticosteroids, rather than new treatment modalities. The first and most important factor is the early diagnosis of RR or NFI. All descriptive studies confirm long-term nerve function is determined by the duration and level of impairment at commencement of therapy for RR. The development of reproducible tests applicable in the field would aid the early recognition of NFI as would the definition of high risk groups with clinical parameters or simple immunological assays. Nevertheless, the education of both staff and patients to recognise the earliest signs of RR will remain the chief operational factor in the diagnosis of RR.

Second, there is still the need to determine the optimal dose and length of therapy with corticosteroids in RR. Current outcomes are not satisfactory as 20–40% of patients in recent studies still failed to recover lost sensation or muscle power. To this end, a double-blinded placebo-controlled trial is underway in referral centres in India to compare the use of observed regimens of prednisolone starting at 60 mg or 30 mg for 20 or 12 weeks (Waters MFR, personal communication). Any future candidate drugs should then be formally compared with the optimal corticosteroid regimen. In addition, the efficacy of corticosteroids inpatients with NFI of >6 months duration needs to be resolved with prospective studies.

Third, the frequency of RR in some patient populations raises the question as to whether prophylactic anti-inflammatory treatment would reduce the frequency of RR and progressive NFI. A community-based double-blinded trial is planned in Bangladesh to address this question by testing the effect of prednisolone 20 mg daily for 6 months on RR and NFI (W. C. S. Smith, personal communication).

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